CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

022460Orig1s000

CHEMISTRY REVIEW(S)

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: **June 10, 2010**

From: **Yichun Sun, Ph.D.**
Review Chemist,
Division of New Drug Quality Assessment II
ONDQA

Through: **Moo-Jhong Rhee, Ph.D.**
Chief, Branch IV
Division of New Drug Quality Assessment II
ONDQA

To: **CMC Review #1 of NDA 22-460**

Subject: **Recommendation for Approval**

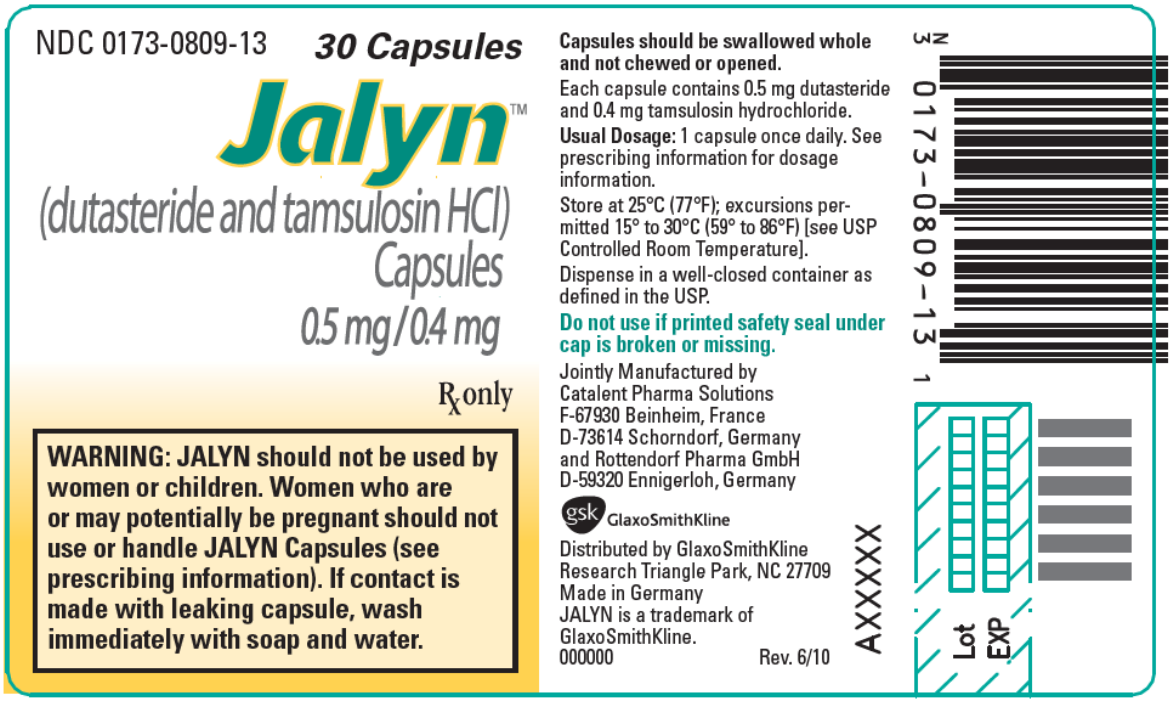
At the time when the CMC memorandum dated January 11, 2010 was written to CMC Review #1, the review on container labels for the NDA was still pending.

On June 7, 2010, the NDA applicant provided the updated container labels. The container labels are reviewed according to 21 CFR 201 and found acceptable (see the review of the labels presented below).

This second memorandum closes all pending issues for this NDA from the CMC perspective and, therefore, this application is now recommended for approval from the CMC perspective.

CMC related information provided for the container labels:

Container label (30 counts)

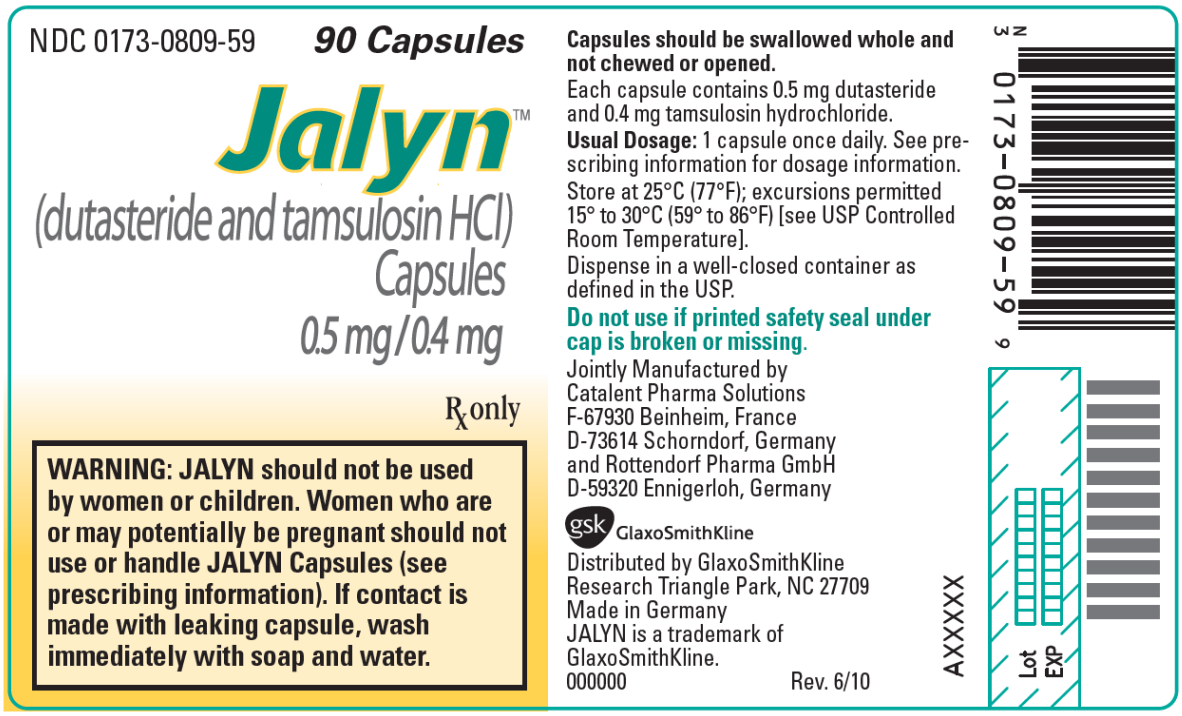


As shown in the above mock-up bottle label, the following items were provided:

- **Proprietary name, established name**
- **Dosage strength**
- **Net quantity of dosage form**
- **"Rx only" displayed prominently on the main panel**
- **Storage conditions**
- **Bar Code**
- **Lot Number**
- **Expiration Date**
- **NDC number**
- **Manufacturer/distributor's name**
- **"See prescribing information for dosage information"**

Evaluation: Acceptable.

Container label (90 counts)

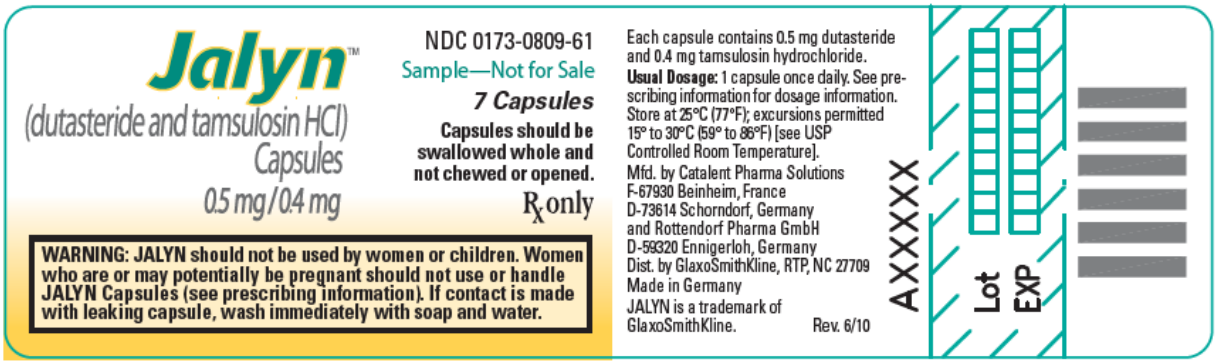


As shown in the above mock-up bottle label, the following items were provided:

- **Proprietary name, established name**
- **Dosage strength**
- **Net quantity of dosage form**
- **“Rx only” displayed prominently on the main panel**
- **Storage conditions**
- **Bar Code**
- **Lot Number**
- **Expiration Date**
- **NDC number**
- **Manufacturer/distributor's name**
- **“See prescribing information for dosage information”**

Evaluation: Acceptable.

Container label (7 counts for sample)



As shown in the above mock-up bottle label, the following items were provided:

- **Proprietary name, established name**
- **Dosage strength**
- **Net quantity of dosage form**
- **"Rx only" displayed prominently on the main panel**
- **Storage conditions**
- **Lot Number**
- **Expiration Date**
- **NDC number**
- **Manufacturer/distributor's name**
- **"See prescribing information for dosage information"**

Note: Bar code is not on the sample container label. However, the bar code requirement does not apply to prescription drug samples according to 21 CFR 201.25 (Bar code label requirements).

Evaluation: Acceptable.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YICHUN SUN
06/10/2010

MOO JHONG RHEE
06/10/2010
Chief, Branch IV

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date: January 11, 2009

From: Yichun Sun, Ph.D.
Review Chemist, ONDQA
Premarketing Assessment Division II
ONDQA

Through: Moo-Jhong Rhee, Ph.D.
Chief, Branch III
Premarketing Assessment Division II
ONDQA

To: CMC Review #1 of NDA 22-460

Subject: Recommendation for Tentative Approval

At the time when the CMC review #1 was written, there were two pending issues: one was the Establishment Evaluation, and the other was issues on the labels.

On January 4, 2009, the Office of Compliance gave an overall "Acceptable" recommendation for all the facilities involved in the manufacture and test of the drug substance and drug product (The EER Summary Report is attached), but the issues on the container labels are still pending.

However, since the this NDA is to be "Tentatively Approval" due to patent issues and the sponsor is to resubmit the NDA when the patent issues are resolved, the labeling issues will be resolved at the second review cycle.

Therefore, this application is recommended for tentative approval from the CMC perspective with pending review on container labels.

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Application:	NDA 22460/000	**Sponsor:**	SMITHKLINE BEECHAM
Org. Code:	580		200 NORTH 16TH ST 1 FRANKLIN PLAZA
Priority:	4		PHILADELPHIA, PA 19102
Stamp Date:	20-MAR-2009	**Brand Name:**	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE
PDUFA Date:	20-JAN-2010	**Estab. Name:**	
Action Goal:		**Generic Name:**	DUTASTERIDE AND TAMSULOSIN HYDROCHLORIDE
District Goal:	21-NOV-2009	**Product Number; Dosage Form; Ingredient; Strengths**	
		001; CAPSULE; DUTASTERIDE; .4MG 001; CAPSULE; TAMSULOSIN HYDROCHLORIDE; .5MG	

FDA Contacts:	J. DAVID	Project Manager	301-796-4247
	Y. SUN	Review Chemist	301-796-1388
	D. CHRISTNER	Team Leader	301-796-1341

Overall Recommendation: ACCEPTABLE on 04-JAN-2010 by E. JOHNSON (HFD-320) 301-796-3334

Establishment:	**CFN:** 1055327 **FEI:** 1000110912		
	CATALENT GERMANY SCHORNDORF GMBH 160 N PHARMA DRIVE		
	MORRISVILLE, NC 27560		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE STABILITY TESTER		
Profile:	CONTROL TESTING LABORATORY	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-APR-2009		
Decision:	ACCEPTABLE		
Reason:	BASED ON PROFILE		

Establishment:	**CFN:** 9615009 **FEI:** 3002806400		
	CATALENT GERMANY SCHORNDORF GMBH STEINBEISSTR. 2		
	SCHORNDORF, , GERMANY		
DMF No:		**AADA:**	
Responsibilities:	FINISHED DOSAGE MANUFACTURER		
	FINISHED DOSAGE PACKAGER		
	FINISHED DOSAGE RELEASE TESTER		
	FINISHED DOSAGE STABILITY TESTER		
Profile:	CAPSULES EXTENDED RELEASE	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	04-JAN-2010		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:** 9615710 **FEI:** 3002808036		
	CATALENT PHARMA SOLUTIONS 67930		
	BEINHEIM, , FRANCE		
DMF No:		**AADA:**	
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
Profile:	CAPSULES, SOFT GELATIN	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	18-DEC-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 9610176 **FEI:** 1000170338		
	GLAXOSMITHKLINE CURRAGHBINNY		
	CARRIGALINE, CO. CORK, , IRELAND		
DMF No:		**AADA:**	N 021319
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
Profile:	NON-STERILE BULK BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	04-JAN-2010		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

Establishment:	**CFN:** 9610419 **FEI:** 3003215057		
	GLAXOSMITHKLINE COBDEN STREET		
	MONTROSE, , UNITED KINGDOM		
DMF No:		**AADA:**	N 021319
Responsibilities:	DRUG SUBSTANCE MANUFACTURER		
	DRUG SUBSTANCE RELEASE TESTER		
	DRUG SUBSTANCE STABILITY TESTER		
Profile:	NON-STERILE BULK BY CHEMICAL SYNTHESIS	**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION		
Milestone Date:	16-APR-2009		
Decision:	ACCEPTABLE		
Reason:	DISTRICT RECOMMENDATION		

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**
Responsibilities:
Profile: **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 02-NOV-2009
Decision: ACCEPTABLE
Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** (b) (4) **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:** (b) (4)
Responsibilities:
Profile: **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 09-APR-2009
Decision: ACCEPTABLE
Reason: BASED ON PROFILE

Establishment: **CFN:** **FEI:** (b) (4)
(b) (4)

DMF No: **AADA:**
Responsibilities: (b) (4)
Profile: **OAI Status:** NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 29-DEC-2009
Decision: ACCEPTABLE
Reason: BASED ON FILE REVIEW

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-JAN-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** 3003732290

ROTTENDORF PHARMA GMBH
OSTENFELDER STR 51 - 61

ENNIGERLOH, , GERMANY

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

Profile: NOT ELSEWHERE CLASSIFIED **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-JAN-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

(b) (4)

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-DEC-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-JAN-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** 3003732290

ROTTENDORF PHARMA GMBH
OSTENFELDER STR 51 - 61

ENNIGERLOH, , GERMANY

DMF No: **AADA:**

Responsibilities: DRUG SUBSTANCE MANUFACTURER

DRUG SUBSTANCE RELEASE TESTER

Profile: NOT ELSEWHERE CLASSIFIED **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 04-JAN-2010

Decision: ACCEPTABLE

Reason: DISTRICT RECOMMENDATION

Establishment: **CFN:** **FEI:** (b) (4)

(b) (4)

DMF No: **AADA:**

Responsibilities:

(b) (4)

Profile: **OAI Status:** NONE

Last Milestone: OC RECOMMENDATION

Milestone Date: 16-DEC-2009

Decision: ACCEPTABLE

Reason: BASED ON PROFILE

FDA CDER EES
ESTABLISHMENT EVALUATION REQUEST
SUMMARY REPORT

Establishment:	**CFN:**	**FEI:**	(b) (4)		
			(b) (3) (B)		
DMF No:				**AADA:**	
Responsibilities:					
Profile:				**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	16-DEC-2009				
Decision:	ACCEPTABLE				
Reason:	BASED ON FILE REVIEW				

Establishment:	**CFN:**	**FEI:**			
			(b) (4)		
DMF No:				**AADA:**	
Responsibilities:			(b) (4)		
Profile:				**OAI Status:**	NONE
Last Milestone:	OC RECOMMENDATION				
Milestone Date:	24-APR-2009				
Decision:	ACCEPTABLE				
Reason:	DISTRICT RECOMMENDATION				

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YICHUN SUN
01/11/2010

MOO JHONG RHEE
01/11/2010
Chief, Branch III

NDA 22-460

FLODART™ (Dutasteride and Tamsulosin hydrochloride) Capsules

GlaxoSmithKline

Yichun Sun, Ph.D.

Review Chemist

Branch III, Division of Pre-Marketing Assessment II
Office of New Drug Quality Assessment

CMC REVIEW OF NDA 22-460
For the Division of Reproductive and Urologic Products
(HFD-580)

Table of Contents

Chemistry Review Data Sheet

1. NDA: #22-460

2. REVIEW #: 1

3. REVIEW DATE: 04-January-2010

4. REVIEWER: Yichun Sun, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
IND 47,838	April 05, 1995
Pre-NDA meeting minutes	October 23, 2008

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original	March 20, 2009
Amendment (BC)	April 01, 2009
Amendment (BC)	May 5, 2009
Amendment (QR)	August 19, 2009
Amendment (QR)	October 2, 2009
Amendment (QR)	November 12, 2009
Amendment (FF)	November 24, 2009
Amendment (BH)	December 22, 2009

7. NAME & ADDRESS OF APPLICANT:

Name:	SmithKline Beecham Corporation d/b/a GlaxoSmithKline
Address:	One Franklin Plaza, 200 North 16th Street, Philadelphia, PA 19102
Representative:	Sherman N. Alfors
Telephone:	(919) 483-5098

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: FLODART™ (Not approved)
b) Non-Proprietary Name (USAN): Dutasteride and Tamsulosin hydrochloride
c) Code Name/# (ONDQA only): N/A
d) Chem. Type/Submission Priority (ONDQA only):

- Chem. Type: 4
- Submission Priority: Standard Review

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (2)

10. PHARMACOL. CATEGORY: 5α-reductase inhibitor (5ARI) and alpha blocker

11. DOSAGE FORM: Capsules, Delayed-release and extended-release

12. STRENGTH/POTENCY: 0.4 mg Dutasteride and 0.5 mg Tamsulosin HCl

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ____ Rx __X__ OTC

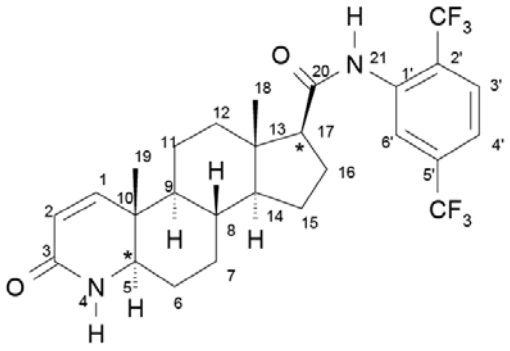
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
_____SPOTS product – Form Completed

___X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Dutasteride

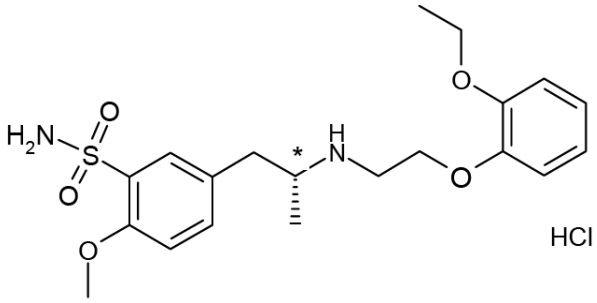
(5α,17β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide



Empirical formula: $C_{27}H_{30}F_6N_2O_2$
Molecular weight: 528.5

Tamsulosin Hydrochloride

R(-)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzene sulfonamide, monohydrochloride



Empirical formula: $C_{20}H_{28}N_2O_5S \cdot HCl$
Molecular weight: 444.97

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE 1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4) 9	II	(b) (4)	(b) (4)	1	Adequate	12/11/2009	NA
14643	II	Catalent Pharma Solutions	Gelatin Preparation for Dutasteride Soft Gelatin Capsules	4	NA	NA	NA
(b) (4)	IV	(b) (4)		1	Adequate	12/11/2009	NA
	III			4	NA	NA	NA
	III			4	NA	NA	NA
	III			4	NA	NA	NA
	III			4	NA	NA	NA
	III			4	NA	NA	NA

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	21-319	AVODART® (Dutasteride) Soft Gelatin Capsules

18. STATUS:

ONDQA:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A	----	----
EES	Pending	----	----
Pharm/Tox	N/A	----	----
Biopharm	Acceptable	12/15/2009	Dr. Sandra Suarez
LNC	N/A	----	----
Methods Validation	N/A	----	----
DMET/DDMAC	N/A	----	----
EA	Categorical Exclusion Acceptable	See Review Date Above	Y. Sun
Microbiology	Acceptable	12/04/2009	Dr. Vinayak Pawar

The Chemistry Review for NDA 22-460

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

This NDA has provided sufficient CMC information to assure the identity, strength, purity, and quality of the drug product. Labels have an issue on the established name and strengths. Also pending is the final recommendation of Establishment Evaluation.

Therefore, from a CMC perspective, this NDA is not recommended for "Approval" in its present form until the Office of Compliance issues an overall "Acceptable" recommendation and the issues on the established name and strength are resolved.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

Two drug substances, Dutasteride and Tamsulosin hydrochloride, are used in the combination drug product (FLODART™ (Dutasteride and Tamsulosin hydrochloride) Capsules) of this NDA. Dutasteride is a chemically synthesized compound. It is the same active pharmaceutical ingredient (API) used in the marketed drug product: AVODART® (Dutasteride) soft gelatin capsules (NDA # 21-319). The FLODART™ (Dutasteride and Tamsulosin hydrochloride) capsules are administered through the same administration route, oral, as AVODART® (Dutasteride) soft gelatin capsules. And the dose of Dutasteride (0.5 mg) in the combination capsule is the same as AVODART® (Dutasteride) soft gelatin capsules dose (0.5 mg). All the information regarding Chemistry, Manufacturing and Controls for Dutasteride drug substance is cross referenced to NDA 21-319. Therefore, the in-process controls and specifications of the drug substance set for AVODART® (Dutasteride) soft gelatin capsules are adequate to ensure the identity, strength, purity and quality of Dutasteride drug substance used in the combination drug product. Tamsulosin hydrochloride is also a chemically synthesized compound. It is the same active pharmaceutical ingredient (API) used in the marketed drug product: FLOMAX® (Tamsulosin hydrochloride) capsules (NDA # 20-579). And the same dose (0.4 mg) of Tamsulosin hydrochloride as FLOMAX® (Tamsulosin hydrochloride) capsules dose is used in the combination drug product. All chemistry, manufacturing and controls information pertaining to Tamsulosin hydrochloride is referenced to the Drug Master File, DMF # (b) (4), held by (b) (4). A letter of authorization is provided. The DMF is reviewed and found adequate.

Drug Product

The drug product, FLODART™ (Dutasteride and Tamsulosin hydrochloride) Capsules, is a pre-printed (b) (4) hard-shell capsule containing one Dutasteride soft gelatin capsule (0.5 mg Dutasteride) and Tamsulosin hydrochloride pellets (containing 0.4 mg Tamsulosin hydrochloride). The pre-printed (b) (4) hard-shell capsules, size 00, have a brown body and an orange cap imprinted with "GS 7CZ" in black ink. The strength of each active component is identical to the commercially available AVODART®, 0.5 mg Dutasteride and FLOMAX®, 0.4 mg Tamsulosin hydrochloride. The capsules are manufactured by encapsulating two intermediate products: a Dutasteride soft gelatin capsule and Tamsulosin hydrochloride pellets, referred to as a Dutasteride Product Intermediate and Tamsulosin Hydrochloride Product Intermediate, respectively. Dutasteride Product Intermediate contains the same dose of Dutasteride as AVODART® (Dutasteride) soft gelatin capsules (b) (4) . The Tamsulosin Hydrochloride Product Intermediate contains the same dose as FLOMAX® (Tamsulosin hydrochloride) capsules (NDA # 20-579). The combination drug product is formulated to be bioequivalent to both commercial AVODART® and FLOMAX® dosed concomitantly. The combination capsule is intended to provide greater convenience to patients and improved compliance, relative to a regimen of two separate dosage units per day.

The drug product, combination capsules, is packaged into opaque, white high density polyethylene (HDPE) bottles with polypropylene child-resistant closures with induction-seal liners.

Based on the submitted stability data, the proposed expiration dating period of 24-month is granted.

B. Description of How the Drug Product is Intended to be Used

FLODART, a combination of Dutasteride, a 5α-reductase inhibitor, and Tamsulosin, an alpha-adrenergic blocker, is indicated for the treatment of symptomatic benign prostatic hyperplasia (BPH) in men with an enlarged prostate. The recommended dose of FLODART is 1 capsule (0.5 mg Dutasteride and 0.4 mg Tamsulosin hydrochloride) taken once daily approximately 30 minutes after the same meal time each day. The capsules should be swallowed whole and not chewed or opened.

C. Basis for Approvability or Not-Approval Recommendation

This NDA provided adequate information on the raw material controls, manufacturing process, specifications, and container/closure. It also provided sufficient stability data to assure identity, strength, purity and quality of the drug product during the expiration dating period.

However, the established name of the drug product and strengths should be separated in the label and the Office of Compliance has not yet issued an overall "Acceptable" recommendation for all the facilities involved.

III. Administrative

A. Reviewer's Signature

/s/ Y. Sun, Ph.D.

B. Endorsement Block

Yichun Sun, Ph.D.
Reviewer _____ Date

Donna Christner, Ph.D.
Pharmaceutical Assessment lead _____ Date

Moo-Jhong Rhee, Ph.D.
Branch Chief _____ Date

Jeannie David, M.S.
Project Manager _____ Date

C. CC Block

131 Page(s) has (have) been Withheld in Full immediately following this page as B4 (CCI/TS)

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-22460	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DUTASTERIDE/ TAMSULOSIN HYDROCHLORIDE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YICHUN SUN
01/04/2010

MOO JHONG RHEE
01/04/2010
Chief, Branch III

Initial Quality Assessment
Branch III
Pre-Marketing Assessment Division II

OND Division:	Division of Reproductive and Urologic Products
NDA:	22-460
Applicant:	SmithKline Beecham, Inc.
Stamp Date:	20-Mar-2009
PDUFA Date:	20-Jan-2010
Trademark:	Flodart
Established Name:	Dutasteride and tamsulosin hydrochloride
Dosage Form:	Capsules
Route of Administration:	Oral
Indication:	Treatment of symptomatic benign prostate hyperplasia (BPH) in men with an enlarged prostate
PAL:	Donna F. Christner, Ph.D.

	YES	NO
ONDQA Fileability:	x	☐
Comments for 74-Day Letter	x	☐

Summary and Critical Issues:

A. Summary

Dutasteride and Tamsulosin Hydrochloride Combination Capsules (DTC), for oral administration, are oblong, hard-shell capsules each containing one oblong, opaque, dull-yellow dutasteride soft gelatin capsule (0.5 mg dutasteride) and white to off-white tamsulosin hydrochloride pellets (0.4 mg tamsulosin hydrochloride). The hard-shell capsules, size 00, have a brown body and an orange cap imprinted with "GS 7CZ" in black ink. They are packed into opaque, white high density polyethylene (HDPE) bottles with polypropylene child-resistant closures with induction-seal liners.

B. Critical issues for review

Adequate information is provided to allow review of the stability data and to set an expiration dating period. However, updated data on the supportive batches manufactured (b) (4) .

Sponsor should clearly state what holding time they are requesting for each intermediate (b) (4) *of the DTC.*

Sponsor (b) (4) *for future commercial batches. This question will be consulted to the Microbiology group for evaluation.*

Sponsor [redacted] *for future commercial batches. This is a review issue.*

C. Comments for 74-Day Letter

Provide updated data on the supportive batches manufactured [redacted]

Please state what holding time you are requesting for each intermediate [redacted] *of the DTC.*

Please be aware that the [redacted] *and* [redacted] *for future commercial batches has been noted and is under review. The microbial limits testing question has been consulted to the Microbiology group for evaluation.*

D. Recommendation:

This NDA is fileable from a CMC perspective. A single reviewer, Yichun Sun, Ph.D. has been assigned. There are two issues to be sent in the 74-day letter.

_____

Donna F. Christner, Ph.D.

NDA Number: 22-460 **Applicant: GlaxoSmithKline** **Stamp Date: 20-Mar-2009**

Drug Name: Flodart **NDA Type: 3S**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	Comment
1	Is the section legible, organized, indexed, and paginated adequately?	X		
2	Are ALL of the manufacturing and testing sites (including contract sites) identified with full street addresses (and CFNs, if applicable)?	X		
3	Is a statement provided to indicate whether each manufacturing or testing site is ready for inspection or, if not, when it will be ready?	X		
4	Is a statement on the Environmental Impact provided as required in 21 CFR 314.50(d)(1)(iii)?	x		Categorical exclusion requested as per 21 CFR 25.31(b)
5	Is information on the Drug Substance provided as required in 21 CFR 314.50(d)(1)(i)?	X		Dutasteride: NDA 21-319 Tamsulosin: DMF (b) (4)
6	Is information on the Drug Product provided as required in 21 CFR 314.50(d)(1)(ii)?	X		
7	If applicable, has all information requested during the IND phases, and at the pre-NDA meetings been included?	X		
8	Have draft container labels and package insert been provided?	X		
9	Have all DMF References been identified?	X		
10	Is information on the investigational formulations included?	X		
11	Is information on the Methods Validation included?	X		
12	If applicable, is documentation on the sterilization process validation included?	X		N/A

IS THE CMC SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the NDA/BLA is not fileable from chemistry, manufacturing, and controls perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Donna F. Christner, Ph.D. 28-Apr-2009

Pharmaceutical Assessment Lead Date

Moo-Jhong Rhee, Ph.D.

Branch Chief Date

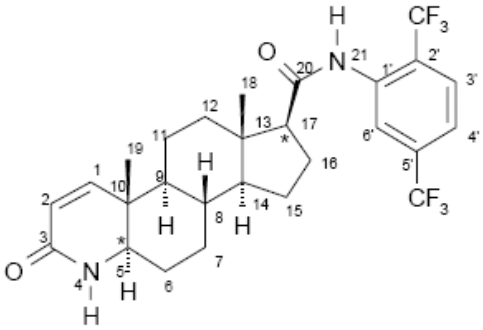
DMF	Holder	Description	LOA	Status
		(b) (4)	Yes	Needs review
14643	Catalent Pharma Solutions	Gelatin preparation for Dutasteride soft gelatin capsules	Yes	
		(b) (4)	Yes	
			Yes	See ONDC Policies on Bottles and Blisters*
			Yes	See ONDC Policies on Bottles and Blisters*
			Yes	See ONDC Policies on Bottles and Blisters*
			Yes	See ONDC Policies on Bottles and Blisters*
			Yes	See ONDC Policies on Bottles and Blisters*

Policy on the Review of Container Closure Systems for Solid Oral Drug Products (Bottles), 26-Apr-2001
Policy on the Review of Blister Container Closure Systems for Oral Tablets and Hard Gelatin Capsules, 29-May-2002

DRUG SUBSTANCE

There are two drug substances in this combination drug product:

DUTASTERIDE



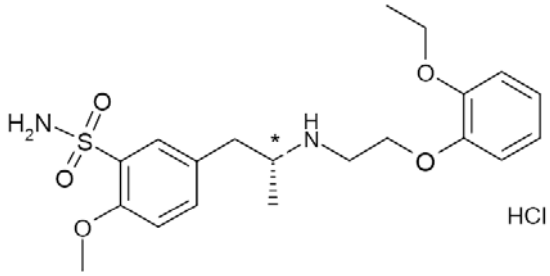
Dutasteride

MW 528.5

5(α,17β)-N-{2,5 bis(trifluoromethyl)phenyl}-3-oxo-4-azaandrost-1-ene-17-carboxamide

Full information on dutasteride in incorporated by cross-reference to the approved AVODART NDA 21-319.

TAMSULOSIN HCl



Tamsulosin Hydrochloride

MW 444.97

R(-)-5-[2-[[2-(2-Ethoxyphenoxy)ethyl]amino]propyl]-2-methoxybenzez sulfonamide, monohydrochloride

Tamsulosin Hydrochloride contains one chiral center and is the R isomer. Full information is provided in DMF (b) (4).

Comment: *DMF* (b) (4) *will require review.*

MANUFACTURERS

The following sites have responsibilities for manufacture of dutasteride and tamsulosin hydrochloride drug substances. This updated information was provided in the 01-Apr-2009 Amendment to the NDA.

eCTD Sequence Number	Site	Function	Registration Number	Site Contact	Telephone Number
Drug Substance - Dutasteride (cross-reference to the approved AVODART® NDA 21-319, amendments, supplements and annual reports thereto)					
-	Glaxo Wellcome Operations Coleden Street Montrose Angus DD10 8EA United Kingdom	Manufacture and quality control testing of dutasteride drug substance	3003215057 FCUK154	Robin Railton Quality Leader	44 (0) 1674 666411
-	SmithKline Beecham (Cork) Limited Currabinny Carrigaline Co Cork, Ireland	Manufacture and quality control testing of dutasteride drug substance	1000170338 FCEI053	Alan J Gray Quality Assurance Director	353 21 4512338
-	(b) (4)				
Drug substance - Tamsulosin Hydrochloride (cross-reference to (b) (4))					
-	(b) (4)				
-					

eCTD Sequence Number	Site	Function	Registration Number	Site Contact	Telephone Number
-	(b) (4)				
-					
-					

Comment: *The facilities were submitted to EES on 09-Apr-2009 by Yichun Sun, Ph.D.*

DRUG PRODUCT

Dutasteride and Tamsulosin Hydrochloride Combination Capsules (DTC), for oral administration, are oblong, hard-shell capsules each containing one oblong, opaque, dull-yellow dutasteride soft gelatin capsule (0.5 mg dutasteride) and white to off-white tamsulosin hydrochloride pellets (0.4 mg tamsulosin hydrochloride). The hard-shell capsules, size 00, have a brown body and an orange cap imprinted with "GS 7CZ" in black ink. They are packed into opaque, white high density polyethylene (HDPE) bottles with polypropylene child-resistant closures with induction-seal liners. The composition of the combination capsules and the drug product intermediates are as follows:

Table 1 Composition of DTC, 0.5 mg Dutasteride and 0.4 mg Tamsulosin Hydrochloride

Component	Quantity (per capsule)	Function	Reference to Standard
Dutasteride Product Intermediate	1 each	Active	GlaxoSmithKline
Tamsulosin Hydrochloride Product Intermediate [1]	(b) (4) mg	Active	GlaxoSmithKline
Pre-printed Hypromellose Hard-Shell Capsule	1 each	Capsule Shell	Supplier

Note:
1. (b) (4)

Table 2 Composition of the Dutasteride Product Intermediate, 0.5 mg Dutasteride

Component	Quantity (mg/capsule)	Function	Reference to Standard
Fill Solution			
Dutasteride [1]	0.50	Active	GlaxoSmithKline
Mono-di-glycerides of Caprylic/Capric Acid (MDC) [1]	(b) (4)		Supplier
Butylated Hydroxytoluene (BHT)			USNF
(b) (4)			-
Gelatin			USNF
Glycerin			USP
Titanium Dioxide			USP
Ferric Oxide, Yellow [2]			USNF
(b) (4)			USP
			-
			Ph.Eur.
			USNF

Note:
1. (b) (4)
2. Ferric Oxide is also referred to as Iron Oxide Yellow.
3. (b) (4)
4.

Table 3 Composition of the Tamsulosin Hydrochloride Product Intermediate, 0.4 mg Tamsulosin Hydrochloride

Component	Quantity (mg/capsule)	Function	Reference to Standard
(b) (4)			
Tamsulosin Hydrochloride [1]	0.400	Active	Supplier
Microcrystalline Cellulose	(b) (4)		USNF
Methacrylic Acid Copolymer Dispersion [2]			USNF
Talc			USP
Triethyl Citrate			USNF
(b) (4)			USP
			-
Methacrylic Acid Copolymer Dispersion [2]			USNF
Talc			USP
Triethyl Citrate			USNF
(b) (4)			USP
			-
			-

Note:
(b) (4)

All compendial excipients are controlled by adherence to compendial specifications. Mono-di-glycerides of caprylic/capric acid (MDC) is a proprietary excipient that is purchased to an agreed specification from an established supplier. Information is cross-referenced to NDA 21-319. Information on **Ferric oxide, yellow** is cross-referenced to NDA 21-319 as well.

According to the Pharmaceutical Development Section, the formulation has been developed so that it is bioequivalent to the approved AVODART and FLOMAX. The Dutasteride intermediate soft gelatin capsule was developed based upon theAVODART formulation. (b) (4)
(b) (4)
(b) (4)
(b) (4) of being filled in a size 00 hard-shell capsule. The Tamsulosin Hydrochloride product intermediate began with a generic Tamsulosin Hydrochloride capsule (submitted by (b) (4), but not approved as a US generic), which contained a pellet of (b) (4)% w/w. The generic formulation was (b) (4) to deliver a 0.4 mg dose, so that the overall weight of the pellets (b) (4)
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6 Page(s) has (have) been Withheld in Full immediately following this page as B4 (CCI/TS)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Donna Christner
5/7/2009 02:51:48 PM
CHEMIST

Hard copy signed by you on 30-Apr-2009

Moo-Jhong Rhee
5/7/2009 03:13:05 PM
CHEMIST
Chief, Branch III